REMARKS

Following entry of the foregoing amendments, claims 1, 15-17, 20, 22, 23, 27, 28, and 36-39 constitute the pending claims in the present application. Applicants have cancelled claim 40, which is rejected as being directed to a non-elected invention. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications. Issues raised by the Examiner are addressed below in the order they appear in the Office Action. Applicants respectfully request reconsideration in view of the following remarks.

1. Applicants acknowledge that a request for continued examination has been granted and that the finality of the previous Office Action has been withdrawn. Applicants also acknowledge that Applicants' previous submission filed on September 12, 2003 has been entered.

2. Applicants note with appreciation the withdrawal of the provisional rejection of claims 1, 15-17, 20, 27, 28 and 36 under the judicially created doctrine of obviousness-type double patenting over claims of copending Application No. 09/708,974.

3. Applicants note that the provisional rejection of claim 21 under the judicially created doctrine of obviousness-type double patenting was rendered moot when the claim was cancelled.

4. Claims 1, 15-17, 20, 22, 23, 27, 28, 36, and 37-39 are rejected under the judicially created doctrine of obviousness-type double patenting over claims of the US Patent No. 6,432,970. Applicants are filing a terminal disclaimer with the instant response. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

5. Applicants note with appreciation that the rejection of claim 21 under the judicially created doctrine of obviousness-type double patenting over claims of U.S. Patent No. 6,432,970 was rendered moot by cancellation of the claim.

6. Applicants note with appreciation the withdrawal of the rejection of claims 1, 15-17, 20, 27, 28, and 36 under the judicially created doctrine of obviousness-type double patenting over the claims of the U.S. Patent No. 6,288,048.

7. Claims 1, 15-17, 20, 22, 23, 27, 28, and 36 are rejected under 35 U.S.C. 112, 1st paragraph, for alleged lack of enablement. Applicants respectfully traverse this rejection.

The Office Action stated that the issue is whether the present specification provides sufficient guidance to enable a skilled artisan to practice the claimed invention commensurate in scope with the instant claims without undue experimentation. Specifically, the Office Action alleged that the specification does not provide a link between the claimed invention and the molecules encompassed by the instant claims. The Office Action takes the position that absent a structural definition of these compounds, a skilled artisan would not know whether use of a given compound falls within the instant claims. The Office Action also stated that any experimentation conducted by a skilled artisan to determine whether a given compound falls in the instant claims constitutes undue experimentation.

Applicants assert, however, that the specification does provide a link between the claimed invention and the molecules encompassed by the instant claims. As a threshold matter, Applicants respectfully point out that structural description of compounds is not a necessary condition or a prerequisite for satisfying the requirements of 35 U.S.C. 112, 1st paragraph. In discussing the requirements of 35 U.S.C. 112, 1st paragraph, the MPEP states that: "one must define a compound by 'whatever characteristics sufficiently distinguish it.'" (See MPEP 2163 quoting Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).) Applicants assert that they have done just that. Namely, Applicants have provided a combination of structural descriptions, e.g., molecular weight of less than 750 amu, and functional descriptions based on how the compounds falling in the present claims behave.

In order to know whether a given compound falls within the instant method claims, a skilled artisan need only check the molecular weight of the compound and its biological activity. Determining the molecular weight of a compound is a trivial matter, squarely within the scope of the knowledge and training of a skilled artisan, e.g., a Ph.D. in chemistry or biochemistry, such as by using a mass spectrometer in a fashion that was routine long before this application was filed. Determining whether a compound interacts with *smoothened* and lessens the severity of a *hedgehog* gain-of-function, *patched* loss-of-function, or *smoothened* gain-of-function phenotype

may be more technically involved, but it is certainly not undue experimentation, because the specification provides a protocol for conducting such an assay (see example 3), and because it is again within the knowledge and training of a skilled artisan to be able to conduct these assays. As such, Applicants assert that the specification provides a link between the claimed invention, and the molecules encompassed by the instant claims.

As to the Office Action's second point that any experimentation conducted by a skilled artisan to determine whether a given compound falls in the instant claims constitutes undue experimentation, Applicants reiterate that such experimentation is routine experimentation and not undue experimentation. The MPEP enumerates at least eight factors that need to be considered when determining whether there is sufficient evidence to support a determination whether any necessary experimentation is "undue". These are: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. (See MPEP 2164.01(a) reiterating factors listed in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).) Applicants address each of these factors separately below.

The breadth of the claims is limited to compounds weighing less than 750 amu that interact with *smoothened* and lessen the severity of a *hedgehog* gain-of-function, *patched* loss-of-function, or *smoothened* gain-of-function phenotype. Applicants assert that the breadth is not at all open-ended, but rather is circumscribed by both structural and functional constraints.

The nature of the invention is tractable to a skilled artisan, e.g., a Ph.D. in bioorganic chemistry or biochemistry. Essentially, the nature of the invention is interaction of a small molecule with a discrete biological target in order to elicit a specified biological response.

The state of the prior art is such that many compounds that bind to and activate or inhibit a biological target were known and widely used at the time the present application was filed. While Applicants maintain that inhibiting unwanted mitotic cell proliferation by administering molecules falling within the instant claims is novel and unobvious over the prior art, the general methodology, i.e., identifying, modifying, and using small molecules to elicit a specified

biological response, was well established in the prior art at the time the instant application was filed.

The level of skill to practice the instant claims is high, i.e., a Ph.D. in bioorganic chemistry or biochemistry. Applicants assert that it is well within the training and knowledge of such an artisan to be able to follow the guidance the specification provides to identify compounds that interact with *smoothened* and can be used to inhibit unwanted mitotic cell proliferation.

The level of predictability in the art is not low. Applicants have provided concrete working examples of molecules falling within the instant claims. Moreover, Applicants point to U.S. Pat. No. 6,552,016, and WO 0311219, patent documents assigned to the present assignee, which show compounds, subsequently identified by assays such as those disclosed in the present application, that also inhibit the hedgehog pathway and are effective on pct-null cells. Thus, Applicants contend that additional compounds can be identified by routine screening with reasonable predictability.

The amount of direction provided by the inventor, and the existence of working examples point against a finding of undue experimentation. Applicants reiterate that they have provided sufficient guidance as to how to identify molecules falling within the instant claims, i.e., in terms of structural and functional descriptors. Moreover, Applicants assert that they have provided a working example of a compound which interacts with smoothened, and inhibits unwanted mitotic cell proliferation. (See example 1 which discloses application of jervine and cyclopamine)

Finally, Applicants assert that the quantity of experimentation needed to make or use the invention is commensurate with the content of the disclosure. Contrary to the position taken by the Office Action, the process of identifying compounds which interact with *smoothened*, is routine and not undue experimentation. The independent claims in the pending claim set necessarily require administering a compound which interacts with *smoothened* or has inhibitory *hedgehog* activity in order to inhibit unwanted mitotic cell proliferation. Thus, Applicants assert that it is necessary for a skilled artisan merely to be able to identify such compounds prior to administering them for the purpose of inhibiting unwanted mitotic cell proliferation. Applicants

have argued above that the specification provides a skilled artisan with the tools necessary to identify and use such compounds.

As stated in MPEP 2164.06, even if the amount of experimentation required is extensive or time consuming, that alone does not make such experimentation undue. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). Applicants submit that the quantity of experimentation needed to make or use the instantly claimed invention is commensurate with the content of the specification.

For these reasons, Applicants respectfully assert that the Office Action's position that a skilled artisan would have had to engage in undue experimentation in order to make and use the instantly claimed invention is untenable. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

8. Applicants acknowledge that the rejection of claim 21 under 35 U.S.C. 112, 1st paragraph, scope of enablement, was rendered moot by cancellation of the claim.

9. Applicants note with appreciation withdrawal of the rejection of claims 1, 15-17, 20, 22, 23, 27 and 36 under 35 U.S.C. 112, 2nd paragraph.

10. Claim 28 is rejected under 35 U.S.C. 112, 2nd paragraph. At issue is the term "prodrug" which appears in the claim. Applicants submit that sufficiently convincing arguments to support inclusion of the term in the claim have been presented in previous Office Action responses, and no corresponding evidence has been provided by the Examiner to support the rejection. Nevertheless, solely to expedite prosecution, Applicants have herein amended claim 28 to

remove the term. Applicants reserve the right to pursue the claim in its unamended form at a later date.

The Office Action also stated that claim 37 is rejected under 35 U.S.C. 112, 2nd paragraph. Applicants assume that the claim is rejected because it depends on claim 28. Applicants submit that the amendment to claim 28 renders moot the rejection of claim 37.

Accordingly, Applicants request reconsideration and removal of the rejection.

12. Applicants acknowledge that the rejection of claim 21 under 35 U.S.C. 112, 2nd paragraph, was rendered moot by the cancellation of the claim.

13. Claims 1, 20, 36, 38 and 39 are rejected under 35 U.S.C. 102(b) over Gerashchenko et al. Applicants respectfully traverse the rejection.

The Office Action stated that Gerashchenko et al. teach a decrease in the proliferation of granulomas formed utilizing jervine, and therefore anticipate the instant claims. (See Gerashchenko et al. on page 3, paragraphs 2-6). Applicants respectfully counter, however, that the proliferation disclosed by Gerashchenko et al. bears no relationship to the unwanted cell proliferation found in the instant claims. Applicants explicitly defined the terms "proliferating" and "proliferation" as referring to cells undergoing mitosis. (See the specification on page 20, line 26.) Applicants point out that the term "proliferation" in Gerashchenko et al. refers not to the mitotic type of cell proliferation, but rather to an aggregative kind wherein different types of phagocytes congregate as part of an inflammatory response to injury, e.g., incisions to the rat's paws, or to the presence of foreign bodies, e.g., cotton pellets, inserted underneath the skin at the incision site. These types of granulomas are consistent with the definition of granulomas formed in response to inflammation. (See STEDMAN'S MEDICAL DICTIONARY - 27th Ed. (2000) which defines this type of granuloma as follows: "a term applied to nodular inflammatory lesions, usually small or granular, firm, persistent, and containing compactly grouped modified phagocytes such as epithelioid cells, giant cells, and other macrophages." (Exhibit A))

The numerous exemplary embodiments Applicants provide regarding mitotic cell proliferation are consistent with Applicant's definition, and are distinguishable from Gerashchenko et al.'s use of the term. For example, on page 44, Applicants disclose how the compounds of the present invention can be used to regulate the proliferation of neuronal stem

cells and neural progenitor cells for the purpose of perpetuating them either *in vitro* or *in vivo*. On page 47, lines 5-15, Applicants disclose how these cells may be incubated in vitro, and their proliferation regulated so as to form neurospheres prior to possible implantation in a heterologous or autologous host for treatment a myriad of diseases where there has been permanent damage to neuronal cells. On page, 49, Applicants disclose that these compounds can be administered to neoplastic or hyperplastic transformations in the central nervous system. Such treatments are useful for treatment of tumors caused by uncontrolled mitotic proliferations such as basal cell carcinoma and medulloblastoma.

In these and other examples Applicants presented throughout the specification, the term "unwanted cell proliferation" is used in the context of unwanted mitotic proliferation and not aggregation of motile phagocytes. Nonetheless, to make clear the distinction between Appplicants' use of the term "proliferation" and Gerashchenko et al.'s use of the same term, Applicants have herein amended claims previously reciting the phrase "unwanted cell proliferation" to "unwanted mitotic cell proliferation". Support for this amendment can be found in the specification at page 20, line 26. Applicants assert that these amendments do not narrow the scope of any of the amended claims because the mitotic nature of the proliferation was already explicit in the definition of the term "proliferation", and therefore was already part of the properly construed claim prior to the amendment.

Applicants assert that the claims as amended are not anticipated by Gerashchenko et al. because Gerashchenko et al. do not teach administering jervine in order to inhibit or decrease mitotic cell proliferation. Accordingly, in light of the reasons and amendments presented above, Applicants request reconsideration and removal of the anticipation rejection.

Applicants further assert that the same reasons and amendments presented above render the instant claims unobvious over Gerashchenko et al. Namely, Gerashchenko et al. do not teach or suggest that jervine can be used to inhibit or decrease unwanted mitotic cellular proliferation. Gerashchenko et al. disclose formation of granulomas in rats' paws in the span of 8 days. As stated above, these granulomas are aggregations of specialized phagocytes in response to the injury inflicted on the rats' paws. There is nothing in Gerashchenko et al. to teach or suggest that jervine would also have a similar inhibitory effect on unwanted mitotic cell proliferation as instantly claimed. Moreover, there is no teaching or suggestion that a similar application of jervine would have an inhibitory effect on tumors and carcinoma. As such, Applicants assert

that one of ordinary skill in the art, having read Gerashchenko et al., would not have had the requisite motivation to administer jervine to unwanted mitotic cell proliferations, or use it for treatment of basal cell carcinoma or medulloblastoma. Applicants further assert that any reasonable expectation of success for such use cannot exist in the absence of teachings in the prior art regarding the efficacy of jervine for inhibiting the mechanistically distinct *mitotic* cell proliferation.

Thus, Applicants assert that Gerashchenko et al. do not render the instant claims obvious. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

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Date: January 29, 2004

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